Appl. No.10/085,612
Amendment dated January 7, 2005
Reply to Advisory Action mailed December 30, 2004

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claims 1-16 (canceled)

Claim 17 (currently amended) A method of screening an individual for predisposition for reduced metabolism of a CYP3A4 substrate ~~or a CYP3A5 substrate~~, said method comprising:

determining the presence or absence in the individual of ~~one or both of~~ a G at position -392 of the promoter of a CYP3A4 gene with respect to the start codon of said CYP3A4 gene; and

~~a G at a position corresponding to nucleotide 1037 in SEQ ID NO:4; and~~

identifying the individual as having a predisposition for reduced metabolism of the CYP3A4 substrate ~~or the CYP3A5 substrate~~ if ~~one or both of~~ the G at position -392 of the promoter of the CYP3A4 gene with respect to the start codon of the CYP3A4 gene ~~and the G at a position corresponding to nucleotide 1037 in SEQ ID NO:4 are~~ is determined to be present in the individual.

Claim 18 (currently amended) The method of Claim 17, wherein said determining comprises, determining whether said individual is homozygous or heterozygous for ~~one or both of~~ the G at position -392 of the promoter of the CYP3A4 gene with respect to the start codon of the CYP3A4 gene ~~and the G at a position corresponding to nucleotide 1037 in SEQ ID NO:4~~.

19.-21. (canceled)

Claim 22 (currently amended) The method of Claim 17, wherein the CYP3A4 substrate is a nitrogen mustard or BCNU ~~and the CYP3A5 substrate is a nitrogen mustard or BCNU~~.

Claims 23-24 (canceled)

Claim 25 (currently amended) A method for selecting a treatment for a cancer patient, said method comprising:

determining the presence or absence in the cancer patient of one or bothmore of a G at position -392 of the promoter of a CYP3A4 gene with respect to the start codon of the CYP3A4 gene; ~~a G at a position corresponding to nucleotide 1037 in SEQ ID NO:4;~~ and a GSTM1 null mutation; and

selecting a treatment selected from the group consisting of:

a treatment that does not comprise administration of an anti-cancer prodrug metabolized to the active drug by CYP3A4 ~~or CYP3A5~~ if ~~one or both of~~ the G at position -392 of the promoter of the CYP3A4 gene with respect to the start codon of the CYP3A4 gene ~~or the G at a position corresponding to nucleotide 1037 in SEQ ID NO:4.~~ is determined to be present in the cancer patient;

a treatment that comprises administration of an anti-cancer prodrug metabolized to the active drug by CYP3A4 ~~or CYP3A5~~ if ~~one or both of~~ the G at position -392 of the promoter of the CYP3A4 gene with respect to the start codon of the CYP3A4 gene ~~or the G at a position corresponding to nucleotide 1037 in SEQ ID NO:4.~~ is determined to be absent in the cancer patient;

a treatment that does not comprise administration of an anticancer drug which is an alkylating agent metabolized by GSTM1 if the GSTM1 null mutation is determined to be absent in the cancer patient; and

a treatment that comprises administration of an anticancer drug which is an alkylating agent metabolized by GSTM1 if the GSTM1 null mutation is determined to be present in the cancer patient.;

~~a treatment that comprises administration of a higher than conventional dose of an anti-cancer prodrug metabolized to the active drug by CYP3A4 or CYP3A5 if one or both of the G at position -392 of the promoter of the CYP3A4 gene with respect to the start codon of the CYP3A4 gene or the G at a position corresponding to nucleotide 1037 in SEQ ID NO:4. is determined to be present in the cancer patient;~~

~~a treatment that comprises administration of a conventional dose of an anti-cancer prodrug metabolized to the active drug by CYP3A4 or CYP3A5 if one or both of the G at~~

~~position -392 of the promoter of the CYP3A4 gene with respect to the start codon of the CYP3A4 gene or the G at a position corresponding to nucleotide 1037 in SEQ ID NO:4, is determined to be absent in the cancer patient;~~

~~a treatment that comprises administration of a higher than conventional dose of an anticancer drug which is an alkylating agent metabolized by GSTM1 if the GSTM1-null mutation is determined to be absent in the cancer patient; and~~

~~a treatment that comprises administration of a conventional dose of an anticancer drug which is an alkylating agent metabolized by GSTM1 if the GSTM1 null mutation is determined to be present in the cancer patient.~~

Claim 26 (currently amended) The method of Claim 25, wherein said determining comprises, determining whether the cancer patient is homozygous or heterozygous for one or both ~~more~~ of the G at position -392 of the promoter of the CYP3A4 gene with respect to the start codon of the CYP3A4 gene~~, the G at a position corresponding to nucleotide 1037 in SEQ ID NO:4,~~ and the GSTM1 null mutation.

Claims 27-29 (canceled)

Claims 30-34 (canceled)

Claim 35 (currently amended) The method of claim 17, wherein the determining comprises: obtaining a genomic DNA sample from the individual; and

performing a PCR amplification reaction on the sample using SEQ ID NO:17 and SEQ ID NO:18 as the ~~one or both of~~ PCR primer pair~~s (a) SEQ ID NO:17 and SEQ ID NO:18 or (b) SEQ ID NO:21 and SEQ ID NO:22.~~

Claim 36 (currently amended) The method of claim 22, wherein the CYP3A4 substrate is the nitrogen mustard~~, and the CYP3A5 substrate is the nitrogen mustard.~~

Claim 37 (previously presented) The method of claim 36, wherein the nitrogen mustard is cyclophosphamide.

Claim 38 (currently amended) The method of claim 22, wherein the CYP3A4 substrate is BCNU, ~~and the CYP3A5 substrate is BCNU.~~

Claim 39 (previously presented) The method of 25, wherein the anti-cancer prodrug is a nitrogen mustard.

Claim 40 (previously presented) The method of 39, wherein the nitrogen mustard is cyclophosphamide.

Claim 41 (previously presented) The method of 25, wherein the alkylating agent is a nitrosourea, a nitrogen mustard or cisplatin.

Claim 42 (previously presented) The method of 41, wherein the nitrosourea is BCNU.

Claim 43 (currently amended) The method of claim 25, wherein ~~the~~ determining the presence or absence in the cancer patient of a G at position –392 of the promoter of a CYP3A4 gene with respect to the start codon of the CYP3A4 gene comprises:

obtaining a genomic DNA sample from the cancer patient; and

performing a PCR amplification reaction on the sample using SEQ ID NO:17 and SEQ ID NO:18 as the ~~one or more of~~ PCR primer pair.~~s: (a) SEQ ID NO:17 and SEQ ID NO:18; (b) SEQ ID NO:21 and SEQ ID NO:22; or (c) SEQ ID NO:23 and SEQ ID NO:24.~~

Claim 44 (currently amended) The method of claim 25, the method comprising determining the presence or absence in the cancer patient of each of the G at position -392 of the promoter of a CYP3A4 gene with respect to the start codon of the CYP3A4 gene~~;the G at a position corresponding to nucleotide 1037 in SEQ ID NO:4;~~ and the GSTM1 null mutation.

Claim 42 (previously presented) The method of 41, wherein the nitrosourea is BCNU.

Claim 43 (currently amended) The method of claim 25, wherein ~~the~~ determining the presence or absence in the cancer patient of a G at position -392 of the promoter of a CYP3A4 gene with respect to the start codon of the CYP3A4 gene comprises:

obtaining a genomic DNA sample from the cancer patient; and

performing a PCR amplification reaction on the sample using SEQ ID NO:17 and SEQ ID NO:18 as the ~~one or more of~~ PCR primer pair~~s: (a) SEQ ID NO:17 and SEQ ID NO:18; (b) SEQ ID NO:21 and SEQ ID NO:22; or (c) SEQ ID NO:23 and SEQ ID NO:24.~~

Claim 44 (currently amended) The method of claim 25, the method comprising determining the presence or absence in the cancer patient of each of the G at position -392 of the promoter of a CYP3A4 gene with respect to the start codon of the CYP3A4 gene~~; the G at nucleotide 1037 in SEQ ID NO:4;~~ and the GSTM1 null mutation.